UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,433	02/02/2006	Lorenzo Frigerio	1009-0118PUS1	8447

2292 7590 01/05/2010

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
01/05/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/535,433	FRIGERIO ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,34-45,48-82 and 84-89* is/are pending in the application.

4a) Of the above claim(s) *45,49,51 and 53-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 34-44, 48, 50, 52, 82, 84-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 34-45, 48-82, and 84-89 are all the pending claims for this application.

2. Claims 46, 47 and 83 were cancelled and Claims 1, 45, 48, 49, 84, and 88 were amended in the Response of 9/11/09.

3. Claims 45, 49, 51 and 53-81 are withdrawn from examination.

4. Claims 1, 34-44, 48, 50, 52, 82, 84-89 are all the pending claims under examination.

5. The finality of this Office Action is withdrawn in view of the Examiner's joining of claims under outstanding rejections. The Examiner thanks Applicants' counsel for pointing out those omissions.

6. Applicants amendment of the claims raises new grounds for objection.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

7. The rejection of Claims 1, 34-44, 48, 50, 52, 82, and 84-87 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

Claim 39 has been joined under this rejection because it depends from Claim 1 and which has not been amended to overcome the rejection as set forth below.

The rejection was maintained in the Office Action of 1/25/08 as follows:

"Applicants' allegations on pp. 15-16 of the Response of 10/31/07 and the Declaration of Dr. Vitale have been considered but are not found persuasive.

In the Response, Applicants allege that a written description rejection should be rare; that the modification is only to be performed on the C-terminal 18 amino acids of the immunoglobulin heavy chain and all of the details for performing the modifications are taught in the specification on pp. 5, 6 and 8-12.

The examiner respectfully submits that any modification can be introduced into the 18 amino acid C-terminus of the heavy chain comprising a α3 or mu domain as the claims are interpreted. This could include, *for example*, any one or all of the modifications to any given nucleotide sequence recited in Claim 35:

a) one or more point mutations
b) one or more nucleic acid deletions
c) one or more nucleic acid additions, *and*
d) one or more nucleotides replaced with a synthetic nucleotide sequence. If a given sequence were to include a modification for each of a-d, then Applicants have not demonstrated a single example of a species falling within the scope much less that the sequence would be reduced in vacuolar targeting signal ability and retain antigen binding activity.

Further, Claim 36 describes another example of a sequence where Xaa2 can be "*any amino acid*" irrespective of its charge, solubility, etc, (and 23 different amino acids exist for each possible substitution) and Applicants have not demonstrated a reasonable number of working embodiments in which "*any amino acid"* could be substituted in the Xaa2 position. A similar comparison can be made to Claims 44 (i.e., X9= *any* amino acid), 45 (Xaa2= independently *any* amino acid), 82 (Xaa2= independently *any* amino acid), and 87 (which depends from Claim 44). Applicants have not demonstrated a reasonable number of species falling within the scope of these claims much less that the sequence would be reduced in vacuolar targeting signal ability and retain antigen binding activity.

The examiner's position is that the specification does not describe a reasonable number of embodiments falling within the scope of generic claim 1 or any one of Claims 35, 36, 44, 45 or 87, and which encodes a heavy chain comprising modified C-terminal 18 amino acids with a reduced or eliminated vacuolar targeting signaling and which still binds an antigen, to support the genus as claimed.

The Declaration of Dr. Vitale is not persuasive on several grounds.

First, Dr. Vitale effectively disavows any priority claim for subject matter of the instant application to the PCT filing date (11/17/2003) and the foreign priority date (11/18/2002). Dr. Vitale asserts that the filing date for the instant application is 5/18/05. It is noted that inasmuch as the instant application entered national stage on 5/18/05, Applicants did not perfect their 102(e) date until 2/2/06 when they filed the executed oath/declaration.

Secondly, Dr. Vitale avers that because only 18 amino acids of the C-terminal end of an immunoglobulin are required to be modified, "there is not an infinite number of possible mutations" and "a sufficient number of representative species of sequences" is demonstrated in the specification.

As discussed in the previous office action and above, Applicants have shown an antibody comprising a modified heavy chain comprising synthetic C-terminal regions for the α3 domain comprising SEQ ID NOS: 7, 8, 9 *or* 69 and comprising a light chain, where the vacuolarization of the heavy chain is reduced or removed when the protein is expressed in transgenic plant cells, and the antibody molecule has specific binding ability for a given antigen in having both a heavy and light chain. Applicants have not shown a reasonable number of antibodies could be produced by the method as falling within the full scope of modifications to the C-terminus encompassed by the instant claims and which would also a) have reduced or removed vacuolarization when expressed in any kind of cell and b) retain antigen binding. For these reasons, the rejection is maintained."

The rejection was maintained in the Advisory Action of 9/11/08 as follows:

"Applicants allege the claims are directed to a method of making antibodies. Applicants allege the rejection is misplaced because the written description for following the method steps is taught in the specification and that in practicing those steps, the specification need not demonstrate that a reasonable number of working embodiments for modified antibodies are actually obtained.

Response to Arguments

The schematic provided in the response on p. 16 outlining the method steps fails to include the final step of screening for functional antibodies, where a functional antibody is required to meet the following criteria a) retains antigen binding, b) the vacuolar targeting signal encoded within the immunoglobulin heavy chain is removed or reduced in its effectiveness, and c) antibody secretion is improved. The data from Figures 6, 7, 9 and 10 shows that examples of C-terminal modified antibodies produced by the method were in fact further examined or screened to see whether antibody secretion was improved (i.e., the transport of the antibody to vacuole was reduced or eliminated). Further, the claim language in Claim 1, element (b) requires that the vacuolar targeting is removed or reduced, and thus absent further screening steps for working embodiments, it is not clear how the ordinary artisan could generate the genus of functional antibodies in view of the broad number of possible modifications introduced into the antibody format in following the method steps."

The rejection was maintained in the Office Action of 3/11/09 as follows:

"Applicants' allegations on pp. 13-14 of the Response of 12/23/08 have been considered and are not found persuasive. Applicants allege "But the Examiner's explanation went on to note that the "data from Figures 6, 7, 9 and 10 [of the Specification] shows that examples of C-terminal modified antibodies produced by the method were in fact further examined or screened to see whether antibody secretion was improved." Applicants submit the Examiner's own comments evidence the impropriety of the continued rejection, in that, the Examiner urges that there is insufficient written description for the claimed method while at the same time the Examiner points to portions of the Specification which indeed describe results of the claimed method."

Response to Arguments

The specification does not describe that in practicing the method, a reasonable number of antibody embodiments falling within the scope of generic claim 1 or any one of Claims 35, 36, 44, 45 or 87 are produced, *and* which comprise a heavy chain comprising modified C-terminal 18 amino acids with a reduced or eliminated vacuolar targeting signaling in plant cells *and* which retain antigen binding. The specification does not support the method for producing the genus of all possible modified antibodies as instantly claimed. As reiterated throughout the examination proceeding, Applicants generic claims specifically recite functional language for the genus of antibodies produced by the method, namely, "to remove, or reduce the effectiveness of, one or more vacuolar targeting signal of the encoded immunoglobulin heavy chain." Thus the ordinary artisan cannot separate the method from the product produced by that method: a) the structure function relationship for the antibodies produced by the method with respect to the modified heavy chain C-terminus, i.e., the modification conferring removal or reduction in the effectiveness of one or more vacuolar targeting signal of the encoded immunoglobulin heavy chain, and b) the ability of the antibody to bind a target antigen. MPEP 2163 states in part:

> "For example, if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. *In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely.* In this latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Compare Fonar, 107 F.3d at 1549, 41 USPQ2d at 1805 (disclosure of software function adequate in that art)."

MPEP 2105 states in part:

> "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical

> and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406", and
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]", and
>
> "A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. See also Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).""

Applicants allegations on pp. 15-16 of the Response of 9/11/09 and the amendments to the claims have been considered and are not found persuasive.

Applicants refer to the decision in *Ex parte Rutanen* (at page 4) for the basic principle underlying the written description requirement. Applicants allege Dr. Vitale specifically states that the specification as filed "provides a sufficient number of representative species of sequences to demonstrate that the invention works across the whole claim genus of sequences" (see paragraph 4 of the Vitale Declaration).

Response to Arguments

The examiner submits that with the exception of the species of C-terminal sequence for the heavy chain shown in Claim 39, and where the heavy chain was co-expressed with a corresponding light chain, that Applicants have not demonstrated a structure/ function correlation for the scope of the claimed antibodies produced by the method. Applicants scope of the antibodies exceeds what they were in possession of at

the time of filing because the scope exceeds the antibodies meeting all of the structural and functional requirements of the claims.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised 3/25/08), support for the claimed invention must be weighed by a combination of the following criteria set forth as: a) actual reduction to practice; b) disclosure of drawings or structural chemical formulas; c) sufficient relevant identifying characteristics such as 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of antibodies; d) a method of making the claimed invention; e) level of skill and knowledge in the art; and f) Predictability in the Art.

Applicants have not demonstrated with sufficient evidence the genus of a functional antibody comprising any heavy chain with any modified α3 or mu domain and any light chain where the heavy chain is directed to any antigen and the light chain is directed to any antigen, and any transgenic plant- or plant cell-expressed antibody having reduced or removed vacuolar targeting by introduction of just any synthetic nucleotide sequence or synthetic tail into the α3 or mu domain of the heavy chain or any α3 or mu domain-modified heavy chain expressed by the host and having retained specific antigen binding affinity in the absence of a corresponding light chain.

The ordinary artisan could reasonably conclude that Applicants were not in possession of the claimed genus of antibodies at the time of application filing.
The rejection is maintained.

Enablement

8. The rejection of Claims 1, 34-44, 48, 50, 52, 82 and 84-89 under 35 U.S.C. 112, first paragraph, is maintained for lacking enablement for expressing a functional antibody comprising any heavy chain with any modified α3 or mu domain and any light chain where the heavy chain is directed to any antigen and the light chain is directed to any antigen, and any transgenic plant- or plant cell-expressed antibody having reduced or removed vacuolar targeting by introduction of just any synthetic nucleotide sequence or synthetic tail into the α3 or mu domain of the heavy chain or any α3 or mu domain-modified heavy chain expressed by the host and having retained specific antigen binding affinity in the absence of a corresponding light chain.

Claim 39 has been joined under this rejection because it depends from Claim 1 and which has not been amended to overcome the rejection as set forth below.

For purposes of review, the rejection was maintained in the Office Action of 1/25/08 as follows:

"A) Applicants' allegations on p. 17 of the Response of 10/31/07 and the Declaration of Dr. Vitale have been considered but are not found persuasive.

Applicants' allege that the specification and the one skilled in the art having a general knowledge such as an undergraduate biology student could practice the invention without undue experimentation.

The examiner submits that because the combination of potential modifications that could be made to the amino acid residues anywhere within the 18 C-terminal residues of a heavy chain comprising an alpha-3 or mu domain is innumerable, and because some residues can be substituted with "*any amino acid*" or the nucleotide encoding the amino acid sequence could comprise one or any combination of

a) one or more point mutations
b) one or more nucleic acid deletions
c) one or more nucleic acid additions, *and*
d) one or more nucleotides replaced with a synthetic nucleotide sequence,

that it would require undue experimentation for one of ordinary skill in the art to practice the invention. More guidance is required for one of ordinary skill in the art to reproduce the invention and render the reproducibility without undue burden.

Further, Applicants have not addressed the predictability factor in Wands which requires that one of skill in the art could predict based on the specification that a reasonable number of antibodies could be produced from any combination of modifications as presently recited in the claims. As discussed above, the specification is not enabling for making the full breath of embodiments where just "*any amino acid*" can be substituted into the C-terminus or the nucleotide encoding the amino acid sequence could comprise one or any combination of

a) one or more point mutations

b) one or more nucleic acid deletions
c) one or more nucleic acid additions, *and*
d) one or more nucleotides replaced with a synthetic nucleotide sequence.

An "undergraduate in biology" could not reasonably expect or predict that the heavy chain produced by the method would have reduced vacuolarization, proper folding with a light chain *and* antigen binding. For example, refer to the references of record describing the unpredictability of amino acid substitutions in protein chemistry in general (Ibragimova and Wade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198); Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138); Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252); Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987); and Lin et al Biochemistry USA Vol 14:1559-1563 (1975)). It is well known in the art that when modifiying an amino acid of a protein, one can expect the 3-dimensional denaturation of the protein.

The specification demonstrates that the NVSVSV sequence is responsible for the vacuolar targeting of the antibodies produced by plants, and more particularly by Nicotania tabacum. Based on the specification, it is not clear whether the NVSVSV sequence has any chance of being recognized by plants other than Nicotiana tabacum. The method of Claim 1 encompasses expressing the antibody in any host cell, but it is not clear from the specification that vacuolar sorting signals would be the same between, for example, mammalian cells, yeast or plants. Absent a showing to the contrary (further experiments or supported reasoning), the specification is only enabling for the modified NVSVSV sequence for use in expressing antibodies, where the host cell is Nicotania tabacum.

B) Applicants have not addressed the section of the Office Action where the examiner rejected the claims on the basis of producing only a single heavy chain antibody. In the Office Action, the examiner asserted that one of skill in the art recognized at the time of Applicant's filing date, that both heavy and light chains, or at least the full complement of CDRs from both a heavy and light chain, were required to be present in an antibody molecule in order for the antibody molecule to bind to the antigen of interest. The rejection was based in the breadth of the claims for producing only a heavy chain in the absence of a corresponding light chain or in the absence of the light chain CDRs. Thus the scope of Applicants claimed method encompasses producing a single heavy chain which allegedly is reduced in vacuolarization and retains antigen binding. Applicants should understand that implicit in producing the antibody molecule with reduced vacuolarization, is the requirement that the antibody molecule have a use under 112, 1st paragraph. It is the examiner's position that the heavy chain produced by the claimed method could not be used and therefore would not have a practical use, i.e., antigen binding, much less that it is unpredictable that the heavy chain alone would bind antigen, thus it is not clear how the claim scope encompassing producing modified single heavy chains would meet the requirements under 112, 1st paragraph.

Applicants' response is incomplete, and therefore the rejection is maintained."

The rejection was maintained in the Advisory Action of 9/11/08 as follows:

"Applicants allege the same rejection was made in Ex parte Kubin. Applicants excerpt Kubin for the aspect of the decision stating "the amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art." Id at 1416. Further, the Hunter et al. publication confirm that vacuole sorting signal sequences work across species.

Response to Arguments

The examiner respectively submits that the facts and the claim scope in Kubin are unlike the instant case. The claims adjudicated in Kubin were directed to polynucleotides encoding polypeptides "at least 80% identical to amino acids 22-221 of SEQ ID NO:2' binding to "CD48." Here instant claim 1 is broader in scope than the claims in Kubin, because in Kubin, the extent of variation could be no more than 20% (or at least 80% identical). Here, there is no limitation as to what constitutes "the modifying" in the region of "the nucleotide sequence encoding the C-terminus 18 amino acids of the immunoglobulin heavy chain molecule." Further, there is no claimed requirement that the final product binds to any antigen. As stated in the Office Action of 1/25/08, the scope of the "modification" encompasses a) one or more point mutations; b) one or more nucleic acid deletions; c) one or more nucleic acid additions, and/or d) one or more nucleotides replaced with a synthetic nucleotide sequence."

The rejection was maintained in the Office Action of 3/11/09 as follows:

"Applicants allegations on p. 14 of the Response of 12/23/08 have been considered but are not found persuasive. Applicants allege "enclosed as Exhibit 1 is a flow chart that details the portions of the Specification that describe the steps of Applicants claimed method in a manner sufficient for one skilled in the art to make and use the claimed invention."

Response to Arguments

Applicants urge the Office to believe that a claimed method is enabled because the specification as summarized in the one page exhibit is fully enabling for practicing the method invention. Additionally, Applicants are wrong in their understanding of the law for enablement under 35 U.S.C. 112, first paragraph. The specification must be enabling for making and ***using*** the invention. Applicants' assertion that the antibodies are not required to have a function much less binding an antigen, or that the method as claimed does not require the product antibodies to have any function, is a legal falsehood. The same antibodies generated by the method must have a utility, otherwise what purpose would be served by practicing the method to produce the polypeptides? See MPEP 2138.05 citing *Birmingham v. Randall*, 171 F.2d 957, 80 USPQ 371, 372 (CCPA 1948) "To establish an actual reduction to practice of an invention directed to a method of making a product, it is not enough to show that the method was performed. "[S]uch an invention is not reduced to practice until it is established that the product made by the process is satisfactory, and [ ] this may require successful testing of the product." The rejection is maintained because Applicants have not met their burden in responding to the grounds for rejection set forth under section A) in the Office Action of 1/25/08.

Applicants have abjectly ignored the Examiner's grounds for rejection set forth under section B) in the Office Action of 1/25/08. The claims read on producing single chain antibodies comprising only a heavy chain and therefore having a single variable domain, that in order to have a practicable use, is otherwise expected to bind an antigen. As stated by the Examiner throughout the prosecution proceeding, there is no enabling disclosure in the originally filed specification or the prior art (see Rudikoff cited in the Office Action of 6/21/07) for a single domain heavy chain antibody which retains antigen binding much less one in which the C-terminus of the heavy chain is modified in the 18 C-terminal, amino acids in order to remove or confer reduced vacuolar targeting of the protein chain in a host plant cell.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding. Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Applicants allegations on pp. 14-15 of the Response of 9/11/09 and the amendments to the claims have been considered and are not found persuasive.

A) Applicants allege that in amending the claims to recite that the modified heavy chain is co-expressed with a light chain would overcome the rejection.

Response to Arguments

Applicants have met only half the burden in responding to this aspect of the rejection. They have amended the generic claims to recite that any host plant cell could

also be induced to co-express a light chain along with the transfected, modified nucleotide sequence for any heavy chain. Just because the host cell is able to express both a heavy and light chain does not address the outstanding issue of there being any functional antibody produced by this method and being capable of binding an antigen.

The claims still read on a single domain antibody whether it is the heavy chain or the light chain. The Examiner has re-iterated over and over during this prosecution proceeding, the art-recognized unpredictability of single domain antibodies having any antigen binding capacity. For a most recent discussion see the Office Action of 3/11/09. Yet despite the technical and legal arguments presented by the Office, Applicants persist in maintaining that the method need only produce an antibody structure recognized by having a light chain and a heavy chain, and irrespective of whether the molecule is functional. The claimed antibodies comprising any heavy chain and any light chain are not required to bind a cognate antigen much less any separate and distinct antigens. Applicants have taken and now advance the position that they are somehow entitled to a new or different level of enablement than what they have otherwise shown in the original specification, by extrinsic evidence or declaration evidence.

B) Applicants next allege “Paragraphs 5-17 of the Declaration of Dr. Frigerio, dated 9 September 2009 (Exhibit 2) specifically address the various points raised by the Examiner in the enablement rejection”; and “As noted in paragraph 11 of the Frigerio II Declaration, the enclosed flow diagram (Exhibit A) summarizes the procedures described in the present application for making antibodies according to the claimed method and paragraphs 12-16 of the Frigerio II Declaration further explain how one

skilled in the art following those procedures could practice the full scope of the claimed invention.

Response to Arguments

The Examiner respectfully submits that the specification and the declaration assuredly define what the structure is on the IgA and/or IgM heavy chain that is intended for modification and the "generic" formula for the domain of Claim 36. However, the ordinary artisan would be forced into undue experimentation to create the myriad modifications to a heavy chain in the area comprising the general formula of Claim 36, transfect the C-terminal modified heavy chains into any plant-based host cell, test for secretion and pair-wise assembly of the modified heavy chain and the plant-based, host cell co-expressed light chain, and then finally characterize the antigen binding ability of the expressed and assembled antibody.

Further, Applicants have ignored the Wands Court discussion of what constitutes a "reasonable" number of working embodiments. Wands does not provide any guidance as to what a reasonable number of working examples should be for an antibody. Specifically the Court stated "No evidence is presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen." Given the state of the art at the time of Wands invention for hybridoma screening, the Court states "This process entails immunizing animals, fusing lymphocytes from immunized animals with myeloma cells to make hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics."

The examiner submits the combination of potential modifications that could be made to the amino acid residues anywhere within the 18 C-terminal residues of a heavy chain comprising an alpha-3 or mu domain is innumerable, and what constitutes a "reasonable" number of modified antibodies having any binding ability that the method should yield, is in fact empirical. The examiner submits that because some residues can be substituted with "*any amino acid*" or the nucleotide encoding the amino acid sequence could comprise <u>*one or any combination of*</u>:

a) one or more point mutations

b) one or more nucleic acid deletions

c) one or more nucleic acid additions, *and*

d) one or more nucleotides replaced with a synthetic nucleotide sequence,

it would require undue experimentation for one of ordinary skill in the art to practice the invention.

The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The rejection of Claims 1, 34, 35, 38, 40, 41, 48 and 50 [*and Claims 84, 85, 88 and 89*] under 35 U.S.C. 103(a) as being unpatentable over Frigerio et al. (Plant

Physiology 123:1483-1493 (August 2000); cited in the IDS of May 18, 2005 and the PTO 892 form of 2/2/07) in view of Vitale and Raikhel (Trends in Plant Science 4(4):149-155 (April 1999); cited in the IDS of May 18, 2005 and the PTO 892 form of 2/2/07), Koide et al. (Plant Cell Physiol. 40(11):1152-1159 (1999); cited in the IDS of and the PTO 892 form of 2/2/07) and Matsuoka et al. (J. Exp. Bot. 50:165-174 (1999); cited in the IDS of 5/18/05) is maintained.

For purposes of review, the rejection was maintained in the Office Action of 1/25/08 as follows:

"Applicants' allegations on pp. 18-19 of the Response of 10/31/07 and the Declarations of Drs. Vitale and Frigerio have been carefully considered but are not found persuasive.

The allegations that are presented are essentially that the named inventors at the time of the instant method invention were the first to realize *and* identify human proteins containing cryptic sorting signals that could be used to target human proteins to a particular location in plants.

The examiner respectfully disagrees with Applicants allegation that no knowledge or awareness of signaling sequences in human proteins existed in the prior art before or at the time of their invention. The knowledge of signaling sequences more especially in view of the Frigerio reference which fully contemplated the existence of cryptic sequence residues that mediated heterologous proteins in vacuole trafficking with the extrapolation of this possibility to the hybrid IgA/G antibodies used in their study belies Applicants assertion. The declarants have not addressed how or why *with* this information in the Frigerio reference, one skilled in the art would not have been motivated to have produced by plant expression methods an antibody that would not be sequestered in vacuoles but instead secreted in abundance by modifying the signal sequences. Thus the rejection is maintained.

The rejection was maintained in the Advisory Action of 9/11/08 as follows:

"Applicants allege element (b) of Claim 1 is not taught in the cited art references.

Response to Arguments

None the individual references taken alone teach the exact language in element (b) of Claim 1 but the claims are not patentably distinguishable in view of the combined disclosures because of the reasons set forth in the Office Action of 6/21/07, and further when considered under the recent KSR decision. Under the recent KSR decision, the cited references of art are not required to "explicitly teach or suggest" all of the steps or elements. The Supreme Court has determined in KSR International Co. v. Teleflex, Inc., 550 U.S._, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not " be led only to those elements of prior art designed to solve the same problem……" (KSR, 550 U.S. at_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82 USPQ2d at 1397) and has further determined that "…….[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that "…… the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at_, 82

USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" ((KSR, 550 U.S. at_, 82 USPQ2d at 1396). "

The rejection was maintained in the Office Action of 3/11/09 as follows:

"Applicants allege on p. 15 of the Response of 12/23/08 element (b) of Claim 1 is not taught in the cited art references. Element (b) recites " (b) Modifying the nucleotide sequence to form a modified nucleotide sequence, wherein the modifying is in the region of the nucleotide sequence encoding the C-terminus 18 amino acids of the immunoglobulin heavy chain molecule to remove, or reduce the effectiveness of, one or more vacuolar targeting signal of the encoded immunoglobulin heavy chain;".

Response to Arguments

Frigerio teaches and appreciates that: "...in tobacco the parent IgG tetramers, which do not have free cysteines, are secreted with high efficiency is consistent with the possibility that thiol-mediated retention also occurs in the plant ER. This hypothesis can be tested by mutagenesis or in vivo treatment with reducing agents." (p. 1489, Col. 1, ¶2); and "Vacuolar Delivery Is Caused by Sequences in the IgA/G Tetramer" (p. 1485, Col. 2, ¶2). Frigerio teaches and appreciates that the C-terminal domains in the heavy chain contribute to this localization event because of their own studies where the k light chain is common to both IgG and and IgA?G heavy chain but differ in the heavy chain.

Vitale and Raikhel teach and appreciate "Sequences that are necessary for sorting some vacuolar proteins have been identified (Table 1). If these sequences are deleted by genetic engineering, the vacuolar proteins are secreted. This is in agreement with the hypothesis that no signal is needed for secretion or, alternatively, it indicates that the vacuolar sorting signals are dominant over unidentified secretion sorting signals. Some of these sequences are also sufficient to determine vacuolar sorting once fused to otherwise secreted proteins, and therefore constitute a complete signal (Table 1)" (p. 149, Col. 1, ¶3). The consensus sequences are found in proteins expressed in plants, and "Clearly, there is no easily identifiable general consensus sequence for vacuolar sorting. However, the situation becomes less complicated if we try to assign the proteins to the two types of clearly identified vacuole, the LV and the PSV. The working model shows that signals with an NPIR-like consensus direct proteins to the LV, whereas the less well-defined signals, which are found at the C-terminus, direct proteins to the PSV" (p. 150, Col. 1, ¶2). Vitale and Raikhel teach and appreciate "It is now clear that most of the features of sorting to plant vacuoles are novel, and might be unique to plants, for example: • The different mechanisms for the two types of vacuoles. • The signals identified. • The potential receptor for LVs and the process of direct delivery from the ER to PSVs. • The aggregation of storage proteins in early compartments of the secretory pathway." Thus the ordinary artisan would have found that in order to express an antibody in a plant host cell that amino acids found in the C-terminus of recombinant proteins such as an antibody, and overlapping or similar to those amino acids ordinarily found in plant proteins associated with or conferring vacuole signal sorting, would contribute to vacuolization rather than secretion of the recombinant antibody in a plant host cell. Further to have considered modifying the 18 C-terminal amino acids in the constant region of the heavy chain, the ordinary artisan would need only to have considered the residues resembling the vacuole signal sorting residues taught by Vitale and Raikhel, Koide and Matsuoka to modify the amino acid residues in order to eliminate or reduce vacuole targeting and increase secreted antibody production.

Applicants' allegations on pp, 16-18 of the Response of 9/11/09 have been considered and are not found persuasive.

A) Applicants now allege "Pages 15 and 16 of the outstanding Office Action set forth the Examiner's attempt to summarize and combine the teachings of the cited references. But missing from the Examiner's discussion is any citation to some portion of one of the cited references that actually teaches step (b) of Applicants' independent

claims, namely the step of modifying the nucleotide sequence in the region of the sequence encoding the c-terminus 18 amino acids of the immunoglobulin heavy chain molecule."

Response to Arguments

The Examiner submits that when Applicants' counsel is not yet able to grasp or comprehend the technical scope of step b) of the generic claims for making any modification to the C-terminal 18 amino acids of the heavy chain, Applicants have placed an onerous and unreasonable burden on the Office to play the role as instructor. The burden of explaining an invention through examination process is seemingly one that would occur between the Applicant and their counsel.

Further, any ordinary artisan (i.e., a person with a master's degree) would understand the infinite breadth of all possible modifications that could be made to the C-terminus and that those modifications could be overlapping with those taught by the prior art of record. Thus where Vitale and Raikhel teach and appreciate "Sequences that are necessary for sorting some vacuolar proteins have been identified (Table 1). If these sequences are deleted by genetic engineering, the vacuolar proteins are secreted", the ordinary artisan would recognize that a "deletion" of a vacuole sorting sequence would be the same as a modification as encompassed by the instant claims.

B) Applicants allege "the new Frigerio II Declaration, at paragraph 18 … further addresses why one skilled in the art would not look for vacuolar sorting signals in antibodies, so that the present invention would not have been obvious to one of ordinary skill in the art."

Response to Arguments

Paragraph 18 (p. 5) in the Frigerio II Declaration states:

"The invention is inventive, because it identifies for the first time a negative correlation between vacuolar sorting and the overall yield of antibody (the crucial information being the secretion of the ΔC18 antibody lacking the vacuolar sorting signal), and it indicates a novel strategy to suppress vacuolar sorting."

The Examiner resubmits where Vitale and Raikhel teach and appreciate "Sequences that are necessary for sorting some vacuolar proteins have been identified (Table 1). If these sequences are deleted by genetic engineering, the vacuolar proteins are secreted", the ordinary artisan would recognize that a "deletion" of a vacuole sorting sequence would be the same as a modification as encompassed by the instant claims.

New Grounds for Objection

Claim Objections

10. Claims 48, 84 and 88 are objected to because of the following informalities:

a) Claims 48 and 84 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Each of claims 48 and 84 depend from Claim 1 and are drawn to identical subject matter.

b) Claim 88, element b) concludes with a period and this appears to be a typographical error since elements c) and d) follow.

Appropriate correction is required.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643